

# Symposium Cont.

## Chronic Urticaria in Children

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### ABSTRACT

*Chronic urticaria (CU) in children often is caused by physical triggers. It also can be associated with autoimmune disease, especially thyroid autoimmunity. Functional autoantibodies against FcεRIα have been reported in children with CU but have not been studied in a systematic fashion. The autologous serum skin test has been proposed as a surrogate test to define the presence of these autoantibodies, although it identifies the presence of histamine-releasing factor, not necessarily antibody. Second-generation antihistamines usually are preferred for chronic therapy. Leukotriene receptor antagonists may be of benefit in a subset of children with CU. (Allergy and Asthma Proc 26:13–17, 2005)*

**A**lthough urticaria occurs commonly in children, the prevalence of chronic urticaria (CU) defined by daily or almost daily wheals with or without angioedema of  $\geq 6$  weeks duration in the pediatric population has not been well defined in cross-sectional studies.<sup>1</sup> For all urticaria-angioedema, prevalence has been reported as 6–7%, but this reflects primarily acute disease. Duration of wheals in CU typically is 6–8 hours, lasting <24 hours and resolving

without any residual skin changes. Patients with CU can have associated delayed-pressure urticaria with pressure-induced lesions lasting longer than 24 hours (although this data is derived from adult patients).<sup>2</sup>

### CAUSATIVE FACTORS

**C**ausative factors in childhood CU have been reported in up to 87% of cases, although this has not always been documented in a convincing manner. In a retrospective study, Kauppinen *et al.*<sup>3</sup> identified a causative factor in 65% of children with CU. In contrast, Harris *et al.*<sup>4</sup> were able to identify an etiology for CU in only 16% of 94 children, again in a retrospective analysis. Of note, in both of these studies, physical urticaria, most commonly cold urticaria, was the most frequently reported cause. Subsequently, Volonakis *et al.*,<sup>5</sup> in a prospective study, found causal factors in 21% of children with CU with physical triggers, again, as the most frequently defined causative factor. Cholinergic and cold urticaria accounted for most of these cases, although dermatographism and pressure urticaria were found also. Although exceedingly rare, both aquagenic and solar urticaria have been described in children.<sup>6,7</sup> Establishing a diagnosis of physical urticaria in children with CU with specific challenge is important because this can limit further evaluation and lead to appropriate intervention.

Other reported causes of CU or recurrent urticaria in children include infections (2–26%), aeroallergens (2%), foods (2–9%), food additives (3–18%), and drugs (2%), although careful review of the literature would suggest that some cases are not confirmed in a convincing manner. In several studies discussed previously,<sup>4,5</sup> ~80% of children with CU were defined as idiopathic; however, these patients were not evaluated for the presence of anti-FcεRI or anti-immunoglobulin E (IgE) autoantibodies (as discussed in the following section, Immune Mechanisms). In addition, CU associated with autoimmune disease in children, although rare, does occur and has been reported as preceding, occurring concomitantly, or appearing after the diagnosis of autoimmune disease.<sup>8</sup> Autoimmune diseases reported in chil-

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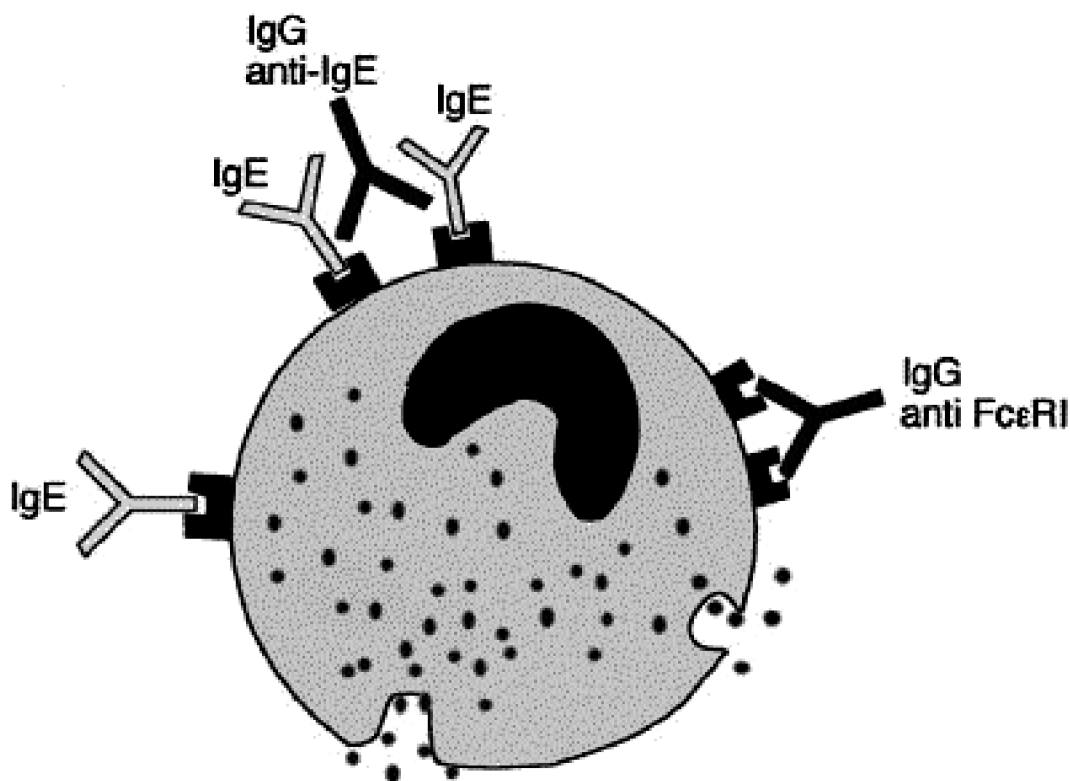
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**Figure 1.** Functional autoantibodies of CU. IgG–anti-IgE antibodies combine with and cross-link adjacent receptor-bound IgE. IgG–anti-FcεRI antibodies combine with and cross-link adjacent α-chains of FcεRI. (Reproduced with permission from Ref. 15.)

dren with CU include thyroid autoimmunity,<sup>8–10</sup> juvenile rheumatoid arthritis,<sup>4,11</sup> insulin-dependent diabetes mellitus,<sup>11</sup> and celiac disease.<sup>12</sup> In their study of CU and thyroid autoimmunity, Leznoff and Sussman<sup>9</sup> reported on 90 patients as young as 8 years of age whose only laboratory abnormalities were tests of thyroid function and thyroid autoimmunity. In a more recent study of 187 children and adolescents with CU, 8 female patients (4.3%) had antithyroid antibodies, with 5 patients being euthyroid and 3 patients hypothyroid.<sup>8</sup> Of note, treatment of the latter three patients did not result in resolution of their urticaria. In contrast, Dreyfus *et al.*<sup>10</sup> described a 9-year-old male child with steroid-resistant CU who had anti-microsomal antibodies but was euthyroid and whose urticaria resolved with thyroid hormone therapy. Because urticaria may precede manifestations of specific autoimmune disease, patients with CU should be monitored for any signs or symptoms suggestive of a specific autoimmune disease, with consideration given to periodic reevaluation of laboratory studies.

## IMMUNE MECHANISMS

A major advance in our understanding of CU has been the demonstration of functional autoantibodies that play a role in the disease of a subset of patients. Grattan *et al.*<sup>13</sup> first reported that a serological factor from certain patients with CU caused development of wheals when injected intradermally and Hide *et al.*<sup>14</sup> identified this factor to be an IgG-class antibody directed against the α-chain of

the high-affinity IgE receptor (FcεRI). Subsequent studies have shown that ~30–40% of adults with CU have anti-FcεRIα autoantibodies, and 5–10% have anti-IgE autoantibodies (Fig. 1; reviewed by Greaves<sup>15</sup> and Kaplan<sup>16</sup>). A functional role for these autoantibodies has been shown by *in vitro* release of histamine from basophils and dermal mast cells.<sup>17</sup> Of note, patients with CU with histamine-releasing autoantibodies have been shown to have more severe urticaria compared with patients with CU without such autoantibodies.<sup>18</sup> Although functional anti-FcεRIα autoantibodies were thought to cause mast cell and basophil degranulation by direct ligation of the α-chain of FcεRI, these autoantibodies were shown subsequently to be primarily IgG1 and IgG3 complement-activating isotypes, suggesting a role for the complement pathway in the pathophysiology of a subset of patients with CU. Kikuchi and Kaplan<sup>19</sup> indicated that IgG autoantibodies could, in fact, directly activate basophils by interacting with the α-subunit of FcεRI, but that histamine release was augmented by serum complement. They subsequently showed that complement activation liberates complement component C5a, which participates in mast cell activation in patients with CU and functional anti-FcεRIα autoantibodies.<sup>20</sup> These findings fit well with the observation that mast cells in the skin express receptor for C5a, and those in the lungs do not.

To date, children with CU have not been studied in a systematic fashion for the presence of anti-FcεRIα autoantibodies.<sup>1</sup> In his review of CU in childhood, Greaves de-

scribed an 11-year-old male child with severe steroid-dependent CU who had documented anti-FcεRIα antibodies.<sup>1</sup> He also listed three other patients ≤16 years with functional anti-FcεRIα autoantibodies.<sup>1</sup> In this author's experience, children presenting for evaluation of their CU who have had documented anti-FcεRIα autoantibodies have not appeared clinically distinct from those children with negative test results for the presence of such autoantibodies and have had variable responses to the treatments discussed in the following sections.

## DIFFERENTIAL DIAGNOSIS

**T**he differential of CU includes urticarial vasculitis, which should be considered if individual lesions last >24 hours. Urticarial vasculitis may be distinguished by palpable purpura as well as bruising or discoloration after urticarial lesions resolve. Normocomplementemic, rather than hypocomplementemic, hypersensitivity vasculitis is more common in pediatric patients. However, cases of hypocomplementemic vasculitis have been reported in children with concomitant systemic manifestations.<sup>21,22</sup> Urticaria pigmentosa, a common form of cutaneous mastocytosis, typically presents as a pigmented maculopapular pruritic eruption that often is widespread and accompanied by a positive Darier's sign.<sup>23</sup> Although urticaria pigmentosa usually is a benign condition, patients can have systemic reactions and, rarely, organ involvement. Papular urticaria, a hypersensitivity reaction to insect bites, typically manifests as grouped or linear wheals or papules.<sup>24</sup>

Muckle-Wells syndrome is an unusual cause of urticarial lesions associated with fever, arthralgias, gradual onset of deafness, and amyloidosis.<sup>25</sup> Recently, Muckle-Wells syndrome, along with a group of inflammatory disorders including familial cold urticaria (more appropriately termed familial cold autoinflammatory syndrome) and chronic infantile neurological cutaneous and articular syndrome, also known as neonatal-onset multisystem inflammatory disease, was shown to result from missense mutations of *CIAS1*, the gene encoding cryopyrin.<sup>26–29</sup> All involve recurrent inflammatory episodes with fever, arthralgia and urticarial-like lesions, which can be the presenting feature.

## EVALUATION

**E**valuation of CU in children is best defined by their history and physical examination and may include specific challenges to identify physical triggers, as well as complete blood count with differential, erythrocyte sedimentation rate, urinalysis, liver function, thyroid function, and antithyroid antibodies. In selected patients, serology for viral hepatitis, serum complement, anti-nuclear antibody titer and specific autoimmune testing, isolation of Epstein-Barr virus in plasma, and stool for ova and parasites may be warranted. Skin biopsy including hematoxylin-eosin and immunofluorescence should be considered if vasculitis or mastocytosis are suspected. Selected allergy evaluation may

be of greater predictive value if negative, while specific challenges and trial of elimination or elemental diet are rarely beneficial in CU. An annotated algorithm for evaluation of CU is described by the Joint Task Force on Practice Parameters.<sup>30</sup> Of note, some studies suggest that children whose CU persists should have yearly reevaluation to rule out late-onset autoimmune disease.<sup>8</sup> At present, documenting the presence of anti-FcεRIα IgG remains an investigative assay fraught with technical problems. Although the autologous serum skin test (ASST) has been proposed as a surrogate or "poor man's" test to define the presence of these autoantibodies, it is important to remember that whealing after intradermal injection of autologous serum identifies the presence of histamine-releasing factor, not necessarily an IgG antibody. The specificity of the ASST in CU as a marker of serum histamine-releasing activity was questioned recently in a study that showed 86% of children with respiratory allergy and 45% of healthy controls with positive ASST.<sup>31</sup>

## TREATMENT

**T**reatment options in children with CU include avoidance of proven provoking stimuli as well as general measures such as avoidance of stress and aggravating factors such as nonsteroidal anti-inflammatory drugs. Although oral (not topical!) H<sub>1</sub>-receptor antagonists have a proven safety and efficacy record and remain useful, especially when dosed at bedtime, second (or third)-generation antihistamines usually are preferred for chronic therapy.<sup>32</sup> Cetirizine is approved for use in children aged 6–23 months (2.5 mg daily), 2–5 years (2.5–5 mg daily or 2.5 mg twice daily), and ≥6 years (5–10 mg daily). Fexofenadine is approved for children aged 6–11 years (30 mg twice daily) and ≥12 years (60 mg twice daily or 180 mg once daily). Loratadine is approved for use in children aged 2–5 years (5 mg daily) and ≥6 years (10 mg daily) and is available without prescription in tablet, rapidly disintegrating tablet, and liquid formulations. Desloratadine (5 mg daily) is approved for patients ≥12 years. Sedating antihistamines including diphenhydramine (5 mg/kg per 24 hours ÷ every [q.] 6 hours) or hydroxyzine (2 mg/kg per 24 hours ÷ q 6 hours) can be added if needed primarily at bedtime in school-aged children. An H<sub>2</sub>-receptor antagonist such as ranitidine (4–5 mg/kg per 24 hours ÷ q. 8–12 hours, maximum 6 mg/kg per 24 hours) may occasionally be of benefit when added to an H<sub>1</sub>-receptor antagonist because H<sub>2</sub>-receptors are present on cutaneous blood vessels. Alternatively, a tricyclic such as doxepin that has both H<sub>1</sub>- and H<sub>2</sub>-receptor blocking activity and a long half-life can be dosed at bedtime because of sedating side effects and the dose can be titrated upward as tolerated. Of note, patients with cold-induced urticaria who are not responsive to the aforementioned antihistamines may respond to cyproheptadine, although parents should be told about the potential for weight gain due to appetite stimulation.<sup>33</sup>

Because leukotrienes including leukotriene C<sub>4</sub> (LTC<sub>4</sub>), LTD<sub>4</sub>, and LTE<sub>4</sub> have been shown to induce wheal-and-flare reactions in patients with CU,<sup>34</sup> leukotriene receptor antagonists have been used to treat CU. Erbagci confirmed the beneficial role of montelukast given 10 mg daily in a single-blind, placebo-controlled, cross-over study of patients with refractory CU, with a decrease in urticaria activity scores and less need for antihistamine rescue therapy while on the leukotriene receptor antagonist.<sup>35</sup> In a different protocol with CU patients  $\geq 12$  years old, only the subset with positive ASST refractory to treatment with cetirizine monotherapy appeared to benefit from addition of zafirlukast to the antihistamine.<sup>36</sup> In a double-blind, placebo-controlled trial that included patients age  $\geq 15$  years old with CU who had positive challenges to aspirin and/or food additives, montelukast (10 mg daily) was shown to be more effective than cetirizine (10 mg daily) or placebo with respect to urticaria scores, preventing interference with sleep and in a median number of days without rescue medication.<sup>37</sup> Montelukast has been approved for children  $\geq 1$  year old and is dosed once daily 4 mg for children 1–5 years old (oral granules are available for children 12–23 months), 5 mg for children 6–14 years old, and 10 mg for those children who are  $\geq 15$  years old. Zafirlukast is approved for patients  $\geq 5$  years old. The dose is 10 mg twice daily for 5- to 11-year-old children and 20 mg twice daily for children who are  $\geq 12$  years old, taken 1 hour before or 2 hours after meals.

Systemic corticosteroids should be avoided, although treatment of delayed-pressure urticaria may require use of oral steroids, which should be tapered to the lowest effective dose, preferably given every other day. Corticosteroid-sparing drugs to consider in pediatric patients include hydroxychloroquine (note that toxicity is dose dependent), although onset of action is slow and data are derived primarily from rheumatology patients. It has been shown to be useful in hypocomplementemic urticarial vasculitis.<sup>38</sup> Other agents in severe, refractory steroid-dependent CU include intravenous  $\gamma$ -globulin<sup>39</sup> and cyclosporin A.<sup>40</sup> Whereas both of these agents are used in pediatric patients, they have not been studied in pediatric CU in a controlled fashion. In the study by O'Donnell *et al.*,<sup>39</sup> 10 patients with CU and positive ASST were treated with intravenous immunoglobulin (400 mg/kg per day for 5 days). Two patients had a sustained remission, three patients relapsed after 6–21 weeks of remission, four patients showed some improvement, and one patient had only minimal, transient improvement. Of note, in the child with steroid-dependent CU with autoantibodies described by Greaves,<sup>1</sup> treatment with intravenous immunoglobulin allowed discontinuation of the oral steroids. Use of thyroxine in euthyroid patients with anti-thyroid antibodies remains controversial.<sup>8,10</sup> Finally, patients with anaphylaxis, including those patients with cold urticaria, should have self-administered epinephrine with appropriate counseling.<sup>41</sup>

## NATURAL HISTORY AND PROGNOSIS

**R**etrospective data suggest that 42% of children with CU followed for  $>1$  year continued to have symptoms.<sup>5</sup> Of the subgroup in whom a presumptive etiologic factor was identified, 73% (11/15) continued to have hives. In a second retrospective study, 50% of children with CU continued to have hives during a mean follow-up of 3.8 years.<sup>4</sup> In a prospective study of infants and children hospitalized with acute urticaria, 30% of cases evolved into chronic or recurrent urticaria at follow-up 1–2 years later.<sup>42</sup>

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